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STUDY ON LOW-DOSE WEEKLY CISPLATIN INDUCED ACUTE TOXICITIES WITH CONCURRENT CHEMORADIATION THERAPY IN HEAD & NECK AND CERVICAL CANCER

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ABSTRACT

Introduction: This study investigates acute toxicities caused by weekly cisplatin in head and neck, and cervical cancer patients. It examines the prevalence rate and risk factors of toxicities, categorizing them to improve understanding and management. **Objectives:** The objective of the present research was to ascertain the frequency rate of acute toxicities induced by weekly cisplatin with concurrent chemoradiation and to categorize the acute toxicities. We also identified the risk factors associated with weekly cisplatin induced acute toxicities. **Materials and Methods:** This prospective observational study investigated the adverse effects of weekly cisplatin with concurrent chemoradiation therapy in 70 patients. The study found that 75.71% developed anemia, followed by leukopenia, neutropenia, and thrombocytopenia. Other adverse effects included dysphagia, alopecia, weight loss, vomiting, diarrhea, constipation, and nephrotoxicity. **Results:** The majority of patients (75.71%) developed anemia, followed by leukopenia (48.51%), neutropenia (37.14%), and thrombocytopenia (27.14%). Most adverse effects were Grade 1, with a few Grade 3 events. A significant association was found between anemia and diagnosis. **Conclusion:** This study emphasizes the importance of monitoring hematological parameters in patients undergoing cisplatin-based chemotherapy to detect and manage adverse effects, improving patient outcomes and minimizing complications. Regular blood count monitoring and patient education are crucial.

KEYWORDS: Cisplatin, head and neck cancer, cervical cancer, CTCAE, acute toxicities, prevalence rate, risk factors.

INTRODUCTION

Head and neck carcinoma comprises epithelial neoplasms located within the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx, with squamous cell carcinoma of the head and neck (SCCHN) representing the predominant variant.[1] Principal risk determinants consist of tobacco usage and alcohol intake, although human papillomavirus (HPV) is increasingly acknowledged for its association with particular subsets of SCCHN.[2] The majority of patients present with disease at an advanced stage, frequently involving regional lymphatic nodes, while the occurrence of distant metastasis at the time of initial diagnosis remains uncommon.[3] The the administration of squamous cell carcinoma of the head and neck (SCCHN) is intricate, necessitating collaboration among various specialists while taking into account factors such as tumor location, disease stage, surgical feasibility, and the overall health of the patient. Conventional therapeutic modalities encompass surgical intervention and radiation therapy, whereas recent innovations have integrated systemic therapies, including epidermal growth factor receptor (EGFR) inhibitors.[4] Survivors of this malignancy encounter prolonged risks associated with cardiac and pulmonary complications, as well as the emergence of secondary primary tumors, frequently associated with persistent tobacco use.[5] Presently, there exists no validated biomarker or recognized chemopreventive agent for SCCHN; however, ongoing investigations into molecular pathways and novel therapeutic agents are progressively enhancing treatment alternatives.[4]

Cervix cells, which are located in the lower part of the uterus that connects to the vagina, are where cervical cancer begins to grow. It is responsible for a sizable portion of the worldwide cancer burden in women. The impact of cervical cancer varies by geography, with literature indicating that more than 85 percent of incidences occur in low- and middle-income nations.[6] With 6,04,127 new cases and 3,41,831 deaths recorded annually, it is the fourth most prevalent cancer diagnosed worldwide and the fourth leading cause of cancer-related deaths among women, according to 2020 predictions.In addition, various other genetic and epigenetic variables contribute to the underlying pathophysiology of cervical cancer.[7]

Cisplatin, commonly known as cis-diamminediachloroplatinum [II] or CDDP, is widely used in the treatment of many human cancers due to its excellent efficacy, as demonstrated by several studies.[8] This medicine has been a cancer treatment staple for over three decades and

is especially effective when taken in combination chemotherapy regimens.[9] Despite its efficiency, cisplatin's clinical use is hampered by the development of cellular resistance and the incidence of significant side effects in normal tissues, as evidenced by multiple research investigations. Cisplatin is a typical treatment for different forms of cancer in pediatric patients, including neuroblastoma, osteosarcoma, and hepatoblastoma, with an 85% cure rate.[10] Notably, cisplatin has shown considerable clinical benefits for those with bladder, head and neck, lung, ovarian, and testicular malignancies, making it an important treatment option.[11] Its major route of action is to impair cell division, which enhances activity in quickly growing cells.[12] Cisplatin's dose-limiting side effects include nephrotoxicity, neurotoxicity, ototoxicity, cardiotoxicity, and, in certain cases, hepatotoxicity.[13]

The relationship between acute toxicities caused by weekly cisplatin and risk factors (age, gender, body surface area, diagnosis, and social history) is examined in this study. Data on hemoglobin, platelets, white blood cells, absolute neutrophil count, and serum creatinine were recorded on the baseline, cycle 3, cycle 5, and following chemotherapy in order to determine the toxicities.

Thus, the purpose of this study was to provide healthcare practitioners with more resources to improve their comprehension of acute toxicities caused by weekly cisplatin. Our study's main goal was to ascertain the prevalence rate of acute toxicities and the risk variables associated with them in patients with cervical and head and neck cancer. Classifying the acute toxicities brought on by weekly cisplatin was the secondary goal.

MATERIALS AND METHODS

The study was a prospective observational study conducted in a tertiary care hospital in Coimbatore, Tamil Nadu. The sample size of 74 was calculated using RAO software from data obtained by daily patient flow and study duration. The study carried out for a duration of 5 months, and data was collected from patients who were administered with the inclusion criteria drug weekly cisplatin with concurrent chemoradiation therapy. The Hemoglobin, Platelet values, Absolute Neutrophil Count, Total Leukocyte Count and Serum Creatinine was obtained and followed up to find the adverse drug events**.** The CTCAE was used to grading the toxicities induced by weekly cisplatin with concurrent chemoradiation. The study was done from March 2024 to August 2024. Chi-squared tests and percentages from SPSS software were used for statistical analysis. The primary outcome showed that 75.71 percent of the 70 patients employed acquired anemia, followed by leukopenia (48.51%), neutropenia

(37.14%), and thrombocytopenia (27.14%). Other adverse effects included dysphagia, alopecia, weight loss, vomiting, diarrhea, constipation, and nephrotoxicity. The majority of adverse effects were grade one, with a few grade three incidents. The secondary outcome revealed a significant correlation between the risk factor of Anaemia with diagnosis (confidence interval: 95%, p-value <0.005).

INCLUSION CRITERIA

- Patients with Age >18 Years.
- Patients with Age < 85 Years.
- Patients with biopsy proven malignancy of Head and neck cancer and Cervical cancer.
- Patients undergoing weekly Cisplatin with concurrent chemoradiation therapy.

EXCLUSION CRITERIA

- Patients under the Age of 18 Years.
- Patients older than 85 years.
- Patients who are not willing to participate in the study.
- Pregnancy and lactation patients.
- Patients with history of Previous Radiation Therapy.
- Patients with history of previous malignancy.

STATISTICAL ANALYSIS

The Statistical Package for Social Science (SPSS) version 26.0 was used to evaluate the data after it was entered into a Microsoft Excel spreadsheet. The chi-squared test was used to compare and analyze quantitative variables.

ETHICS

The study was approved by institutional Human Ethics Committee, PSG hospitals, Coimbatore, Tamil Nadu, India. (Approval no: PSG/IHEC/2024/Appr/Exp/008; approved on March 22, 2024. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and /or national research committee and with the and 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

In this study, 70 patients were recruited based on their inclusion and exclusion criteria. The age wise distribution was found by grouping the patients into 18-30 years with (1.43 %), age

group 31-50 years with (27.14 %), age group 51-70 years with (64.29 %), and above 70 years with (7.41 %). The gender wise distribution emphasizes male of 44.29 % and female of 55.71 %. The study categorizes BMI as less than 18.5 (underweight) with 21.4 %, 18.5 – 24.9 (normal range) with 52.4 %, 25 - 30 (overweight) with 20 % and more than 30 (obese) with 4.2 %. Among total population the social history was taken into consideration and 15.71% (n=11) were smokers, 14.28%(n=10) were Alcoholics, 14.28% (n=10) were both smokers and alcoholics and 55.71% (n=39) patients were none. The diagnosis wise distribution shows Head and Neck cancer patients were 43% (n=40) and Cervical cancer patients were 57% (n=30).

In this study, 12 ADR's were found among 70 patients. **(Table 1)** shows prevalence rate of ADR's. Those Objective were calculated according to the Prevalence rate,

$$\text{Prevalence rate} = \frac{\text{No of new cases of Adverse effects}}{\text{Total study population}} \times 100$$

Table 1: Prevalence rate of occurred ADR's in study population.

Adverse Drug Effects	Prevalence Rate
Anaemia	75.71 % (n=53)
Leukopenia	48.51 % (n=34)
Neutropenia	37.14 % (n=26)
Thrombocytopenia	27.14 % (n=19)
Dysphagia	22.85 % (n=16)
Alopecia	17.14 % (n=12)
Weight loss	34.28 % (n=24)
Weight gain	7.14 % (n=5)
Vomiting	27.14 % (n=19)
Diarrhoea	24.28 % (n=17)
Constipation	12.85 % (n=9)
Nephrotoxicity	21.42 % (n=15)

In this study, The ADR's were categorized based on CTCAE (Common Terminology Criteria for Adverse Events). The results showed Anaemia with Grade 1 being the most common (52.83%, n=28), Leukopenia with Grade 3 was most frequent (44.11%, n=15), Neutropenia with most cases being Grade 1 (63.38%, n=17). Thrombocytopenia with Grade 1 being the most common (57.89%, n=11), Dysphagia with Grade 2 being most common (56.25%, n=9), Alopecia with Grade 1 being the most common (91.66%, n=11). Weight Loss (34.28%, n=24), Constipation (12.85%,n=9) and Weight Gain (7.14% ,n=5) all falls under Grade 1. Vomiting (94.73%, n=18), Diarrhoea (76.47%, n=13) and Nephrotoxicity (66.66%,n=10)

with Grade 1 was most frequent. **(Figure 1)** depicts the relationship of anaemia with diagnosis showed significant statistical association. Patients with cervical cancer were more susceptible to developing toxicities. The remaining ADR's did not demonstrate a statistically significant correlation.

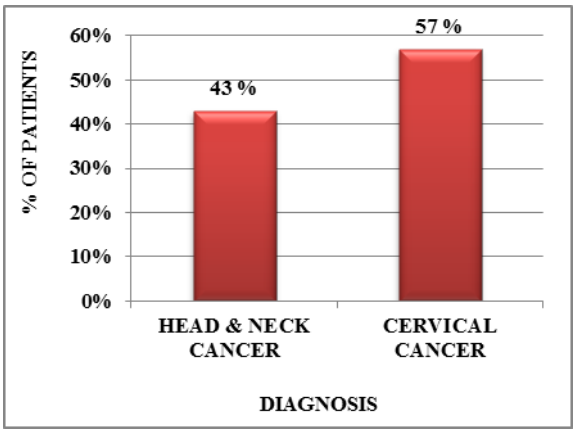

Figure 1: Relationship of anaemia with diagnosis.

DISCUSSION

The study offers insights into the clinical and demographic characteristics of patients receiving weekly chemoradiation with cisplatin. It highlights the treatment's efficacy and potential for both haematological and non-haematological toxicities. The study found that the most individuals with head and neck and cervical malignancies were older women. Cisplatin-based chemotherapy is commonly used to treat head & neck and cervical malignancies. Cisplatin is commonly used in various cancer types due to its radio-sensitizing qualities and therapeutic efficacy (P B Chougule et al.,).[14] supporting this observation. The study found that the majority of patients had a normal BMI. Some patients were underweight, overweight, or obese, which may impact treatment tolerance and outcomes. Previous research indicates that malnutrition and severe BMI levels can negatively effect chemotherapy tolerance and survival in cancer patients (J Arends).[15] A minority of patients reported smoking or consuming alcohol, which aligns with recognized risk factors for head and neck malignancies, particularly squamous cell carcinoma (Hashibe et al.,).[16] Lifestyle variables can influence cancer growth, treatment side effects, and prognosis.

The CTCAE system was used to categorize adverse drug reactions (ADRs) in patients receiving weekly Cisplatin with concurrent chemoradiation therapy for head and neck cancer and cervical cancer. The most common grades were 1, 2, and 3. There are no Grades 4 or 5 that require medical attention. The study found a significant decrease in hemoglobin, total

leukocyte, neutrophil, and platelet counts throughout the therapy period. Cisplatin-based chemotherapy, recognized for its myelosuppressive effects, can cause anaemia, leukopenia, neutropenia, and thrombocytopenia. Anaemia was a prevalent adverse event, consistent with the literature. Chemotherapy-induced anaemia is a well-documented consequence of cancer treatment, leading to fatigue and poor quality of life (Groopman et al.,).[17] The majority of haematological toxicities were mild to moderate, while more severe instances were uncommon but nevertheless clinically significant. Leukopenia and neutropenia, albeit less prevalent than anaemia, require constant monitoring due to the increased risk of infections caused by low white blood cell counts (Lustberg et al.,).[18] Thrombocytopenia was less common but still a worry due to the risk of bleeding problems. In addition to haematological toxicities, non-haematological side effects have been recorded. Common side effects of cisplatin and radiation therapy were dysphagia, baldness, vomiting, and weight loss. Dysphagia, or difficulty swallowing, is a major problem for head and neck cancer patients undergoing chemoradiation. It can lead to malnutrition, dehydration, and poor quality of life (Cristofaro et al.,).[19] Cisplatin can cause alopecia, which is typically reversible after discontinuing treatment (Rossi et al.,).[20] Cisplatin has a high emetogenic potential, which can lead to vomiting even with antiemetics. Weight loss was more common than weight gain, highlighting the need for dietary support throughout therapy to maintain body weight and overall health. A small number of individuals may gain weight due to fluid retention or treatment-induced metabolic changes. The patient's diagnosis increases the risk of anemia, while age, gender, BMI, and social history have no significant impact on the likelihood of getting anemia. Neutropenia, thrombocytopenia, leukopenia, dysphagia, and nephrotoxicity do not correlate with age, gender, BMI, diagnosis, or social history.

The study highlights the importance of complete patient management during cisplatin-based chemoradiation. This includes regular monitoring of haematological markers and proactive control of adverse effects. Anaemia and other haematological toxicities highlight the need for supportive care measures such blood transfusions and erythropoiesis-stimulating medications to enhance patient outcomes and keep therapy on track. Non-haematological side effects like dysphagia and vomiting emphasize the need for a multidisciplinary approach in managing these patients, including oncologists, dietitians, speech therapists, and other healthcare specialists. According to (Islam et al.,).[21] taking a holistic approach to treatment can reduce side effects, improve patient quality of life, and increase treatment effectiveness.

LIMITATIONS

The study was performed in a single-center hospital that resulted in homogenous sample intake. The follow-up of patient's files and collecting sample details were difficult, due to record unavailability. The study was conducted with a limited number of samples, reducing the statistical power to detect significant risk factors.

CONCLUSION

This study highlights the significance of monitoring hematological parameters in patients undergoing cisplatin-based chemotherapy, as it can lead to a range of adverse effects, including anemia, leukopenia, neutropenia, and thrombocytopenia. Regular blood count monitoring is crucial for early detection and management of these effects, improving patient outcomes. While the overall safety profile of cisplatin is acceptable, hematological toxicities must be closely monitored to ensure timely interventions and minimize complications.

Healthcare providers should prioritize regular monitoring of hematological parameters to promptly identify and address adverse effects. Patients should be educated on the importance of reporting any symptoms or side effects during chemotherapy treatment. Further research is needed to develop predictive models that can identify patients at high risk of developing myelosuppression and allow for personalized therapy. The use of novel therapies and molecular information can help mitigate the risks of chemotherapy-induced myelotoxicities. Pharmacists play a crucial role in improving appropriate medical care, reducing the occurrence of myelosuppression, and optimizing chemotherapy regimens. Medication chart review, follow-up, and adverse drug reaction monitoring are essential components of chemotherapy management.

Author's contributions

Anitha A, Aadharshini G Madhulika Vijayakumar were involved in concept, design, definition of intellectual content, literature search, data acquisition, statistical analysis, manuscript editing, and manuscript preparation. Prudence A Rodrigues helped in clinical studies, data analysis,, statistical analysis, and manuscript review. The manuscript has been read and approved by all authors and all the requirements have been met.

Conflict of Interest

None declared.

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